Great Expectations: Harnessing the Power of Tetrathiafulvalene

C500 Final Report

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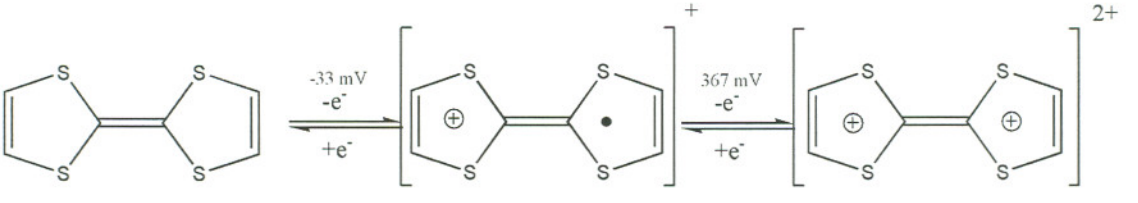
Introduction/Background

Since its discovery 35 years ago,[1] tetrathiafulvalene (TTF) has inspired great interest from researchers. The molecule has unique properties, which, if fully understood and controlled, could serve many purposes. A simple literature search reveals a wide range of applications in which researchers are using TTF and its derivatives. Originally, they were prepared for the development of electrically conducting materials like molecular wires and organic metals. In the years following, the utility of TTF derivatives was discovered as a building block in macrocyclic and supra-molecular chemistry as redox-active systems.

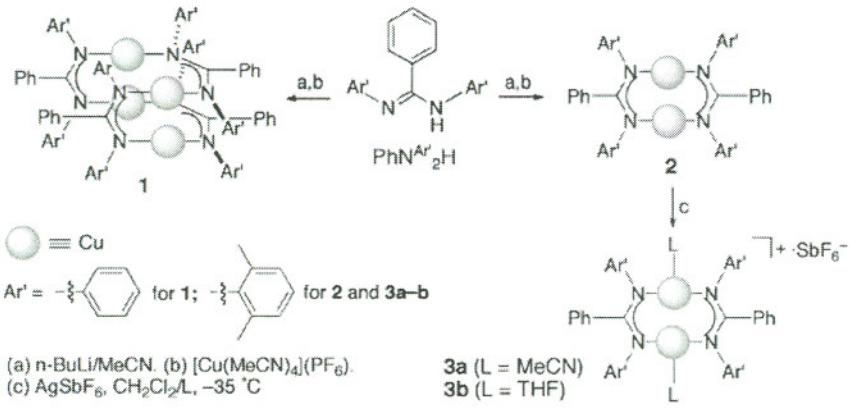
Perhaps the most interesting property of TTF is its sequential and reversible one-electron redox processes as shown in Scheme 1.[2]



Scheme 1. Sequential one-electron oxidations of TTF afford stable cationic species

TTF possesses redox properties comparable to those of inorganic molecules like ferrocene. The first oxidation occurs at -33 mV with respect to Fc/Fc^{+}, an easily obtainable range for observing redox processes.[3] The stability of this compound as a ligand and its use as a charge transfer material[4] should allow us to probe the electronic effects of the ligand on transition metal clusters. Our group has recently established reliable synthetic routes to dimeric or tetrameric copper clusters by varying the steric

bulk of the supporting ligands (Scheme 2).[5] By varying the steric bulk of the N-substituted aryl groups, dimer or tetramer formation could be controlled.



Scheme 2. Synthesis of Copper Amidinate Complexes

Few TTF-substituted transition metal complexes have been reported,[6] making it desirable to open this new and exciting field of TTF chemistry using current findings from our group.

TTF compounds have also shown to be useful in synthesizing supramolecular structures. TTF dendrimers[7] have been synthesized, as well as smaller "belt" structures and cyclophanes.[2] These structures are exciting to chemists of because the potential for an electroactive TTF system to demonstrate interesting host/guest interactions. Systems like those shown in Figure 1 show promise in the field. The ability to encapsulate a guest in a larger host molecule is intriguing and chemists interested in charge transfer between donor and acceptor are sure to explore these TTF containing systems.

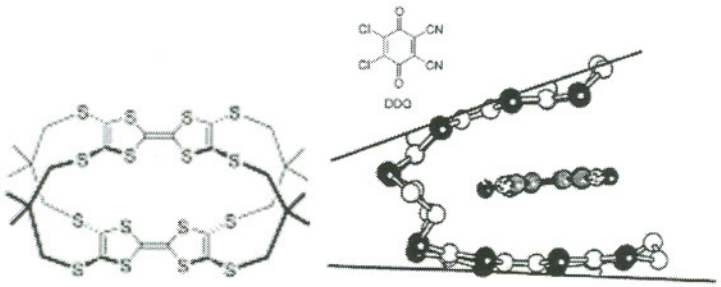


Figure 1. TTF cages and cyclophanes.

Finally, modified TTF units has shown promise in the field of organic conductors. Bis(ethylenedithio)tetrathiafulvalene salts (BEDT-TTF) containing trihalide ions form polymorphous solids that can structurally adjust between semiconductor, metallic, and superconductor properties. This results in good conductivity from low (≤185K) to high (≥395K) temperatures.[8] An example of a TTF containing organic conductor is shown as Figure 2.

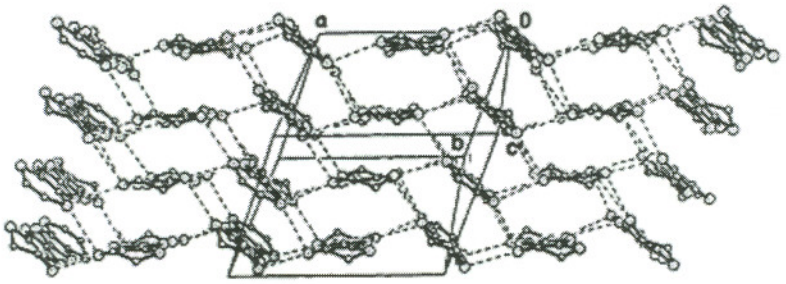


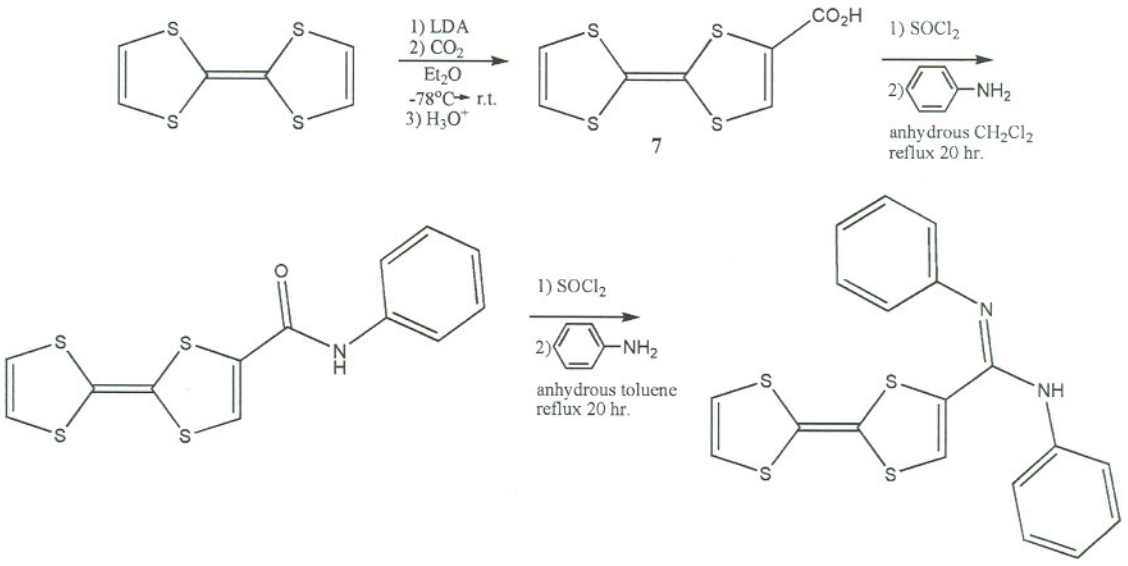
Figure 2. A molecular conductor (in cationic salt form): Bis(ethylenedithio)tetrathiafulvalene

Chemists interested in molecular wires will obviously consider incorporating TTF as a charge transporting unit because of its previous and potential success in such applications.

Objectives

The first objective of this C500 project was to master the large-scale synthesis of TTF. Once made, we then aimed to study its electrochemical properties, its

derivatization to previously unknown ligands that can bind transition metal ions, and its ability to facilitate communication between multiple redox-active centers. Once transition metal complexes could be synthesized, we aimed to oxidize one TTF ligand and evaluate electronic communication through bonds or space between the two ligands. The oxidation potential is expected to be much higher for the oxidation of the second TTF ligand if it is electronically coupled to the first oxidation. Scheme 2 shows the synthetic routes toward the target molecule. We thought that once we had made and isolated the amidine, we could easily complex it to a copper system following the previously reported procedure by our group. [4]



Scheme 3. A proposed synthetic route to TTF-amidine.

Additionally, we hypothesized that TTF could promote tautomerization of a C_3-symmetric core: 1,3,5-triformylphloroglucinol. A change from *keto-enamine* to *enol-imine* should occur from electrochemical stimuli (Figure 4).

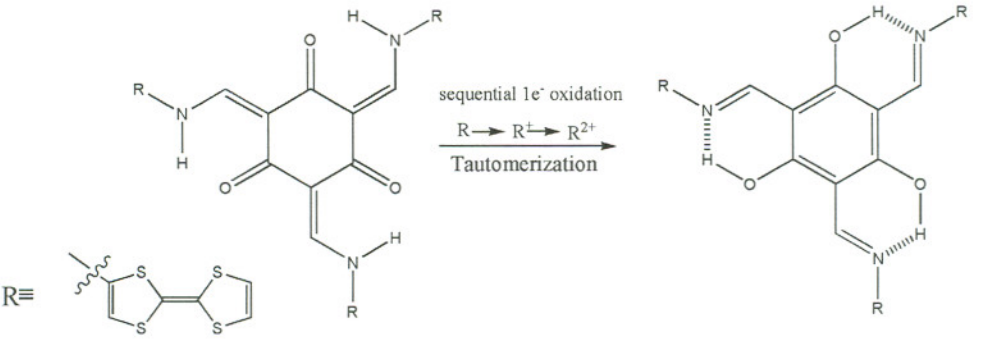


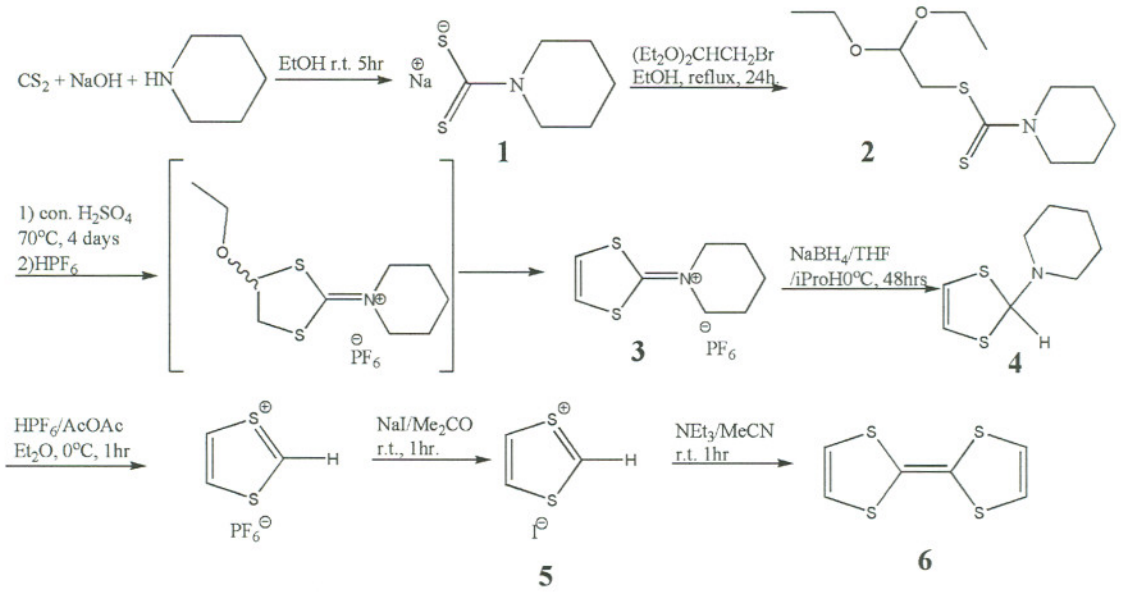
Figure 4. Electrochemically controlled tautomerization

With sequential oxidations of TTF, the acidity of the enamine proton will be affected and at a specific oxidation state, proton transfer is expected to occur,[9] resulting in tautomerization, a formal transfer of hydrogen atoms accompanied by a switch of adjacent conjugated double bonds. The tautomerization should be observable through infrared spectroscopic methods by the disappearance of the carbonyl peak, and the appearance of a new alcohol peak.

The utility of triggered tautomerization is that it demonstrates an external control over a desired physical property, in this case, a rearrangement from one isomer to another. Previously, tautomerization has been triggered using lasers, variable temperatures, and electrochemical methods.[10,11]

Results and Discussion

The large-scale synthesis of TTF has previously been reported (Scheme 4).[12]



Scheme 4. Synthesis of tetrathiafulvalene

Moore and coworkers developed a method of preparing up to 20 g of TTF in 7 steps from readily available starting materials. The lowest yielding step is 76%. The published procedure requires about two weeks of synthesis, however, in our first two attempts, we observed even longer times needed for the desired product. Optimizing the procedure is crucial because of the expense of TTF, where 25 g of material costs about $3,000.[13] The electrochemistry of the unsubstituted TTF was studied and the resulting cyclic voltammogram (CV) is shown in Figure 5. The first oxidation occurs at -33 mV and the second at +367 mV.[14] The peak to peak separation of the first redox coupled wave is 150 mV and the second is 140 mV. The anodic and cathodic peak currents are of equivalent magnitude. We can safely classify TTF as possessing sequential and reversible one electron oxidative properties.

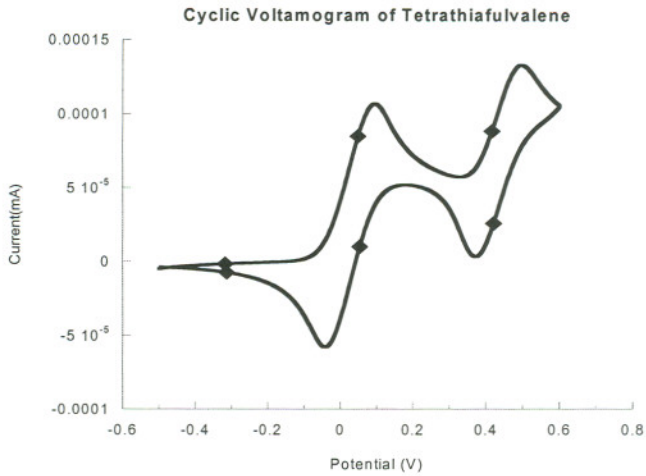
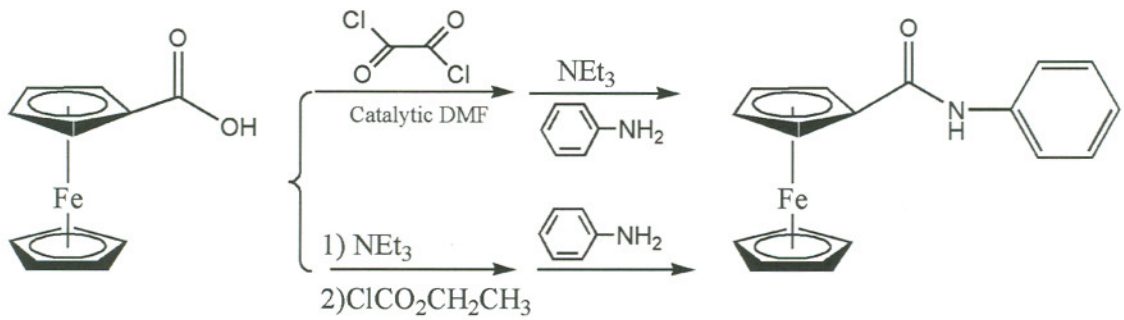


Figure 5. Cyclic voltammogram of TTF (vs. Fc/Fc^{+}) reveals sequential and reversible redox processes.[15]

Optimizing the reactions to afford a TTF-amidine is important. Because of their similar properties as redox-active species, ferrocene was used as a model system. Both have well defined redox active processes. Starting from ferrocene monocarboxylic acid, ferrocene-amidophenyl was prepared following the reaction sequence detailed in Scheme 5.



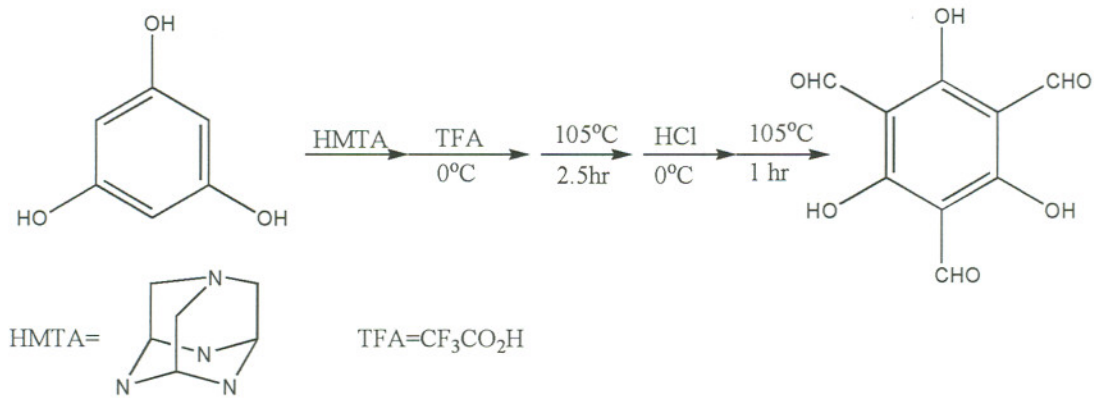
Scheme 5. Synthesis of ferrocene-amidophenyl.

A total of four methods were attempted to synthesize the target. The first required oxalyl chloride. A second method used ethyl chloroformate[16]. The third published account used thionyl chloride[17], and the fourth procedure used freshly

prepared PPSE[18], each starting with ferrocene monocarboxylic acid. The ethyl chloroformate route was successful in producing the amide, a pale red/orange solid, but the yields were much lower (16%) than that obtained from the oxalyl chloride method (88%). The thionyl chloride route produced black oil in each attempt, as did the PPSE method. Characterization of these two reaction products revealed no product. Both reactions that produced product were carried out at room temperature, whereas the thionyl chloride route required reflux temperatures, making the oxalyl chloride method most preferred.

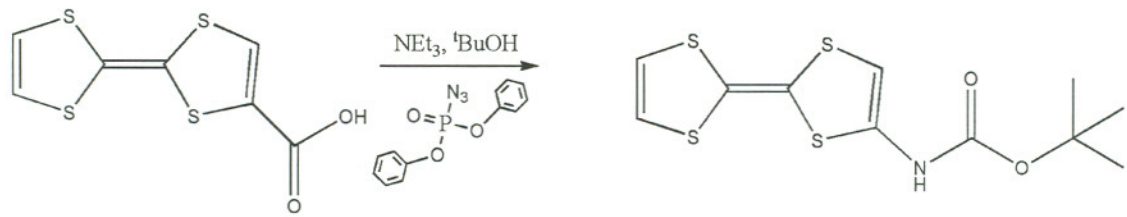
According to Scheme 3, once synthesized, the amide should easily be converted to the amidine. However, this was not the case. Reaction of the amide with thionyl chloride followed by addition of 1 equivalent of amine resulted in a black oily residue similar to the product encountered in amide synthesis by thionyl chloride. Reaction of the amide with PCl_5[19] followed by addition of an equivalent of amine resulted in a final product of white solid that showed no solubility in any solvents. The only published method of synthesizing ferrocene amidine we found that we did not attempt used t-BuLi and DCC[20] because it gives no tunability in substituents of the amidine, something we need to be able to control.

For the tautomerization study, the core was synthesized using the procedure detailed in Scheme 6.[21]



Scheme 5. Synthesis of C_3 1,3,5-triformylphloroglucinol

In order to attach TTF to the core, and obtain the *keto-enamine* in Figure 5, TTF-amine was required, the synthesis of which has not been reported. Our goal was to synthesize tBOC-protected amine derivatives following the Curtius rearrangement seen in Scheme 5.[22] Once made, the tBOC group can be removed in situ to affort the desired amine.



Scheme 6. Synthesis of ^{t}Boc-protected TTF amine.

To date, the protected amine has not been synthesized, but the TTF-monocarboxylic acid has been synthesized and characterized.[23] The ^{1}H-NMR spectrum of this compound is shown in Figure 6.

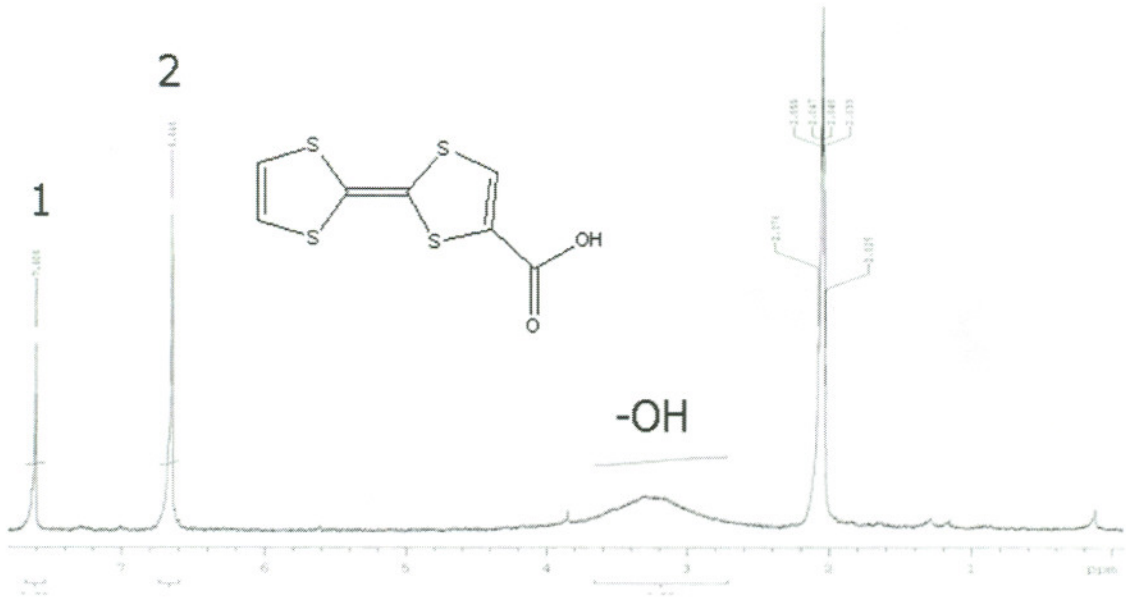


Figure 6. ^{1}H NMR of TTF-monocarboxylic acid in d_6-Acetone.

Experimental Section

General Considerations

Reactions were performed using flame or oven dried glassware and common Schlenk line techniques. All NMR spectra were recorded with a Varian Gemini 2000 (300MHz ^{1}H) at room temperature and referenced to residual solvent peaks. Unless otherwise noted, all chemicals were commercially available and used without further purification. Alfa-Aesar supplied bromoacetaldehyde diethyl acetal, and ferrocene monocarboxylic acid. Acetic anhydride was purchased from Mallinckrodt. Activated carbon was purchased from Fisherbrand. Carbon disulfide and trifluoroacetic acid was purchased from EMD. Oxalyl chloride was purchased from ACROS organics. All other chemicals were purchased from Sigma-Aldrich. Solvents were saturated with nitrogen and purified by passage through activated Al_2O_3 columns under nitrogen (Innovative Technology SPS 400).

Sodium Dithiocarbamate (1). To an ice cooled 3-necked 500 mL round bottom flask fitted with a mechanical stirrer containing 200 mL ethanol was added 40 mL (0.4 mol) piperidine and the mixture stirred for 15 min at 0 °C. To the solution, NaOH pellets (16 g, 0.4 mol) were added over a period of 10 min at 0 °C. A portion of CS_2 (24 mL) was added over a period of 20 min using an addition funnel. With addition, the reaction mixture changed from a colorless solution to a pale yellow/white cloudy suspension, which was stirred at 0 °C for 1 h. After a period of 20 min, the mixture turned thick white foam. The reaction was heated at reflux and stirred for 3 h to furnish a yellow liquid layer and a solid white precipitate **(1)**. The solid material was isolated by filtration and used without purification.

Formylmethyl Piperidine-1-carbodithioate Diethyl Acetal (2). To a reaction flask containing **1**, bromoacetaldehyde diethyl acetal (60 mL, 0.4 mol) was added dropwise using an addition funnel over a period of 15 min to afford a dark red solution. The reaction mixture was refluxed for 24 h and cooled to r.t. A portion of H_2O (650 mL), was added to quench the reaction and the product extracted into dichloromethane (1.1 L). Organic fractions were combined, washed with brine solution, dried over anhyd magnesium sulfate, filtered, and volatile fractions were removed to afford a dark brown oil, which solidified upon standing. Recrystalization from hexane afforded the product **2** as a tan solid material (94.11 g, 85%). ^{1}H NMR ($CDCl_3$): δ = 4.659 (t, 1H), 4.28 (bs, 2H), 3.91 (bs, 2H), 3.74-3.62 (m, 2H), 3.58 (q, 4H), 1.67 (bs, 6H), 1.20 (t, 6H).

2-Piperidino-1,3-dithiolium Hexafluorophosphate (3). A portion of concentrated H_2SO_4 (75 mL) was stirred for 10 minutes at 0 °C in a 1 L 3-necked round bottom flask fitted with mechanical stirrer. A portion of **2** (94.11 g, 0.340 mol) was

added to the flask over 25 minutes at 0 °C. The reaction mixture was stirred at 70 °C for a period of 5 days. After cooling to r.t. the suspension was poured into a stirred solution (250 mL) of HPF_6 (76 g. 0.31 mol, 60% w/w in H_2O kept at 0 °C). Upon addition, a very thick grey solid formed which was isolated by filtration and dissolved into CH_2Cl_2. The solution was concentrated to ca ½ of its initial volume to induce crystallization. Diethyl ether (150 mL) was added to promote further crystallization. The solid material was filtered and washed with diethyl ether. ^{1}H-NMR analysis showed a mixture of the desired product **3** and its intermediate species. The solid was subjected to the H_2SO_4 procedure described above and stirred an additional day at reflux. The reaction contents were isolated following the same procedure, then washed with brine solution, dried over anhyd magnesium sulfate, filtered and volatile fractions removed until point of crystallization. Diethyl ether (150 mL) then added. A white solid material was collected by filtration, washed with diethyl ether, and dried in vacuo overnight to afford **3** (47.9 g, 48%).

^{1}H NMR (acetone-d_6) δ = 7.72 (s, 2H), 4.02 (t, 4H), 1.97 (m, 4H), 1.84 (m, 2H).

2-Piperidino-1,3-dithiole (4). A portion of **3** (47.9 g, 0.145 mol) was suspended in a mixture of THF/^{i}PrOH (1:1, v/v, 400 mL). A portion of $NaBH_4$ (5.52 g, 0.146 mol) was added over a period of 2.5 h. Solution became tan in color and more transparent. The reaction mixture was stirred at 0 °C for 3.5 h, contents warmed to r.t., and stirred for 60 h. The volume was reduced to 250 mL, and H_2O (250 mL) was added. Contents extracted by diethyl ether (250 mL), washed with brine, dried over anhyd magnesium sulfate, filtered, and volatile fractions were removed to afford **4** as a bright

orange oil which crystallized upon standing at r.t. (21.19 g, 78%). ^{1}H NMR: ($CDCl_3$) δ = 6.29 (s, 1H), 6.14 (s, 2H), 2.45 (t, 4H), 1.51 (m, 4H), 1.40 (m, 2H).

1,3-Dithiolium Iodide (5). A portion of acetic anhydride (150 mL) was stirred at 0 °C under N_2 for 20 min in a 3 necked round bottom flask fitted with a mechanical stirrer. A portion of HPF_6 (66 g, 60% by weight) was added over a period of 35 min at 0 °C. The reaction was extremely exothermic. The color of the solution became pale yellow colored following addition. The mixture was diluted with diethyl ether (100 mL) and stirred for a period of 30 minutes at 0 °C. The off-white solid was collected by filtration and dried in vacuo 30 min to afford 24.51 g of 1,3-dithiolium hexafluorophosphate. This solid was dissolved in dry acetone[24] and stirred under N_2. A portion of NaI (14.81 g, 0.988 mol) in dry acetone was added to the solution to precipitate a yellow solid. The solid was collected by filtration and washed with acetone and diethyl ether to afford 5 (20.35 g, 90%). This solid material darkens at 125 °C and melts at 138 °C. ^{1}H NMR: (DMSO-d_6) δ = 9.44(s, 2H). Product was also characterized by mass spectrometry (ESI, CI methods: μ-I^-=103.97 amu observed, 102.97 amu calculated).

Tetrathiafulvalene (6)

A portion of **5** (20.35 g, 0.088 mol) was suspended in CH_3CN (250 mL) under N_2. A portion of triethylamine (13.7 mL, 0.98 mol) was added by syringe over a period of 15 min. Upon addition, the suspension turned from bright yellow to dark green to black. The mixture was stirred for 1 h at r.t. and treated with H_2O (900 mL) to afford a dark yellow solid, which was collected by filtration. The crude solid was dissolved in CH_2Cl_2, washed with brine, dried over anhyd magnesium sulfate, and filtered. The

filtrate was concentrated to afford an orange solid which was collected, dissolved in boiling cyclohexane (350 mL) and treated with activated carbon (≈10g). The suspension was filtered and the filtrate stored at -35 °C overnight to afford orange needles of **6**, which were collected by filtration and dried in vacuo (yield = 5.11 g, 57%).

^{1}H NMR: ($CDCl_3$) δ= 6.31 (s)

Tetrathiafulvalene monocarboxylic acid (7). A portion of 6 (1.18 g, 5.77 mmol) was dissolved in anhydrous diethyl ether (35 mL) in a 100 mL round bottom flask. The solution was cooled to -78 °C and stirred for 10 min. To this cooled solution, lithium diisopropylamide (2 M solution in THF, 3.18 mL, 6.35 mmol) was added by syringe over a period of 8 minutes to darken the solution from bright orange to brown/orange color. The reaction mixture was stirred for 90 min at -78 °C. Dry CO_2 was bubbled through the mixture for 60 min to afford a yellow solid suspension, which was warmed to r.t. overnight (16 h). An orange solid was isolate by filtration, washed with diethyl ether, and suspended in DI H_2O (35 mL).Upon acidification with 2N HCl (15 mL) a thick red solid precipitate was immediately afforded. This red solid was collected by filtration and extracted into CH_2Cl_2 (800 mL). The solution was washed with brine solution, dried over magnesium sulfate, filtered, and volatile fractions were removed to afford a red/violet powder of **7** (0.82 g, 65%). ^{1}H NMR (acetone-d_6): δ = 7.606 (s, 1H), 6.646 (s, 2H), 3.24 (bs[25]).

Ferrocene-amidophenyl.

a. Ethyl chloroformate route

A portion of ferrocene monocarboxylic acid (0.42 g, 1.83 mmol) was dissolved in dry acetone (40 mL) and cooled to 0 °C with stirring under N_2. To this solution was added triethylamine (0.31 mL, 2.19 mmol) and the solution stirred for 10 min. Upon addition, the color changed from bright orange to darker orange. A portion of ethyl chloroformate (0.21 mL, 2.19 mmol) was added by syringe and the reaction mixture stirred for 3 h at 0 °C. A portion of aniline (0.80 mL, 8.7 mmol) was added by syringe and the reaction mixture heated to 45 °C and stirred overnight (16 h). Volatile fractions were removed and the remaining residues dissolved in CH_2Cl_2 (200 mL), washed with brine solution, 2N HCl, and saturated $NaHCO_3$ solution. The organic layer was dried over anhyd magnesium sulfate, filtered, and concentrated to afford product. Recrystallization from hexanes/ethyl acetate affords 0.07g (yield=13%) ferrocene-amidophenyl. ^{1}H NMR: ($CDCl_3$) δ = 7.602 (d, 2H), 7.410 (bs, 1H), 7.342 (t, 2H), 7.108 (t, 1H), 4.769 (s, 2H), 4.406 (s, 2H), 4.237 (s, 5H).

b. Oxalyl chloride route

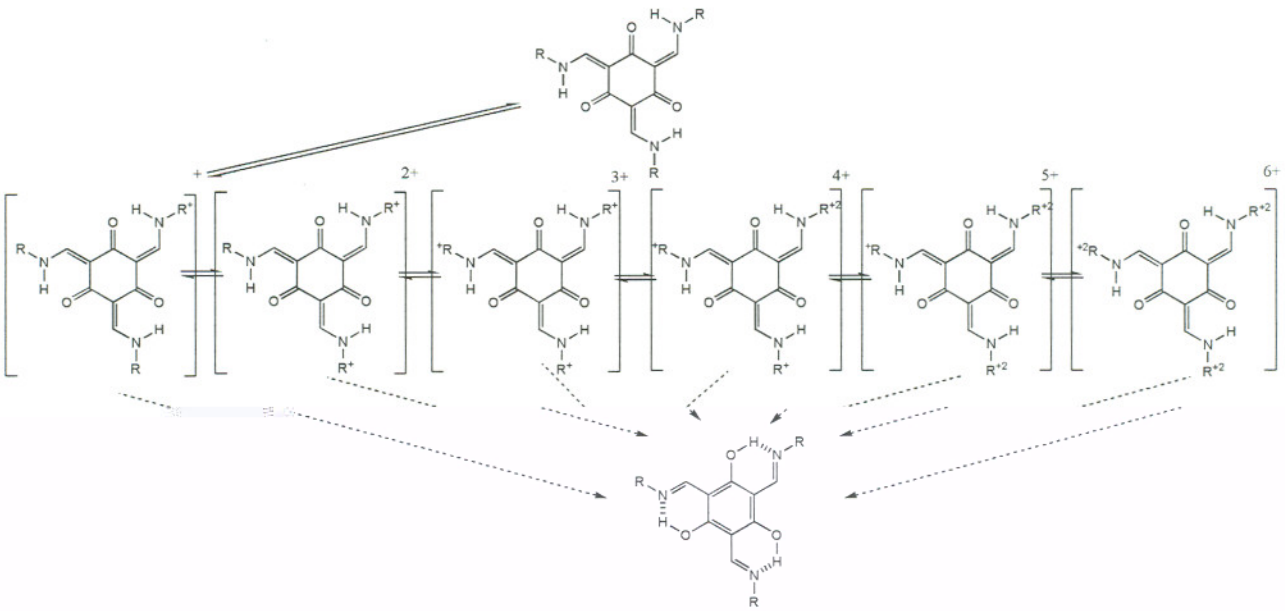
A portion of ferrocene monocarboxylic acid (0.50 g, 2.17mmol) was dissolved in anhyd CH_2Cl_2 under N_2 and treated with oxalyl chloride (1.54 mL, 17.4 mmol) and 1 drop of DMF. The color of the mixture changed from bright orange to deep red. The reaction mixture stirred at r.t. for 60 min under N_2 and then volatile fractions removed in vacuo. In a separate round bottom flask was prepared a mixture of triethylamine (0.33 mL, 2.39 mmol) and aniline (0.22 mL, 2.39 mmol) in CH_2Cl_2 (250 mL). This mixture was added to the residues and stirred at r.t. overnight (16 h). Volatile fractions were removed to afford an orange waxy solid (0.48 g, 76%) orange waxy solid which was characterized by ^{1}H NMR and confirmed by x-ray crystallography.[26] ^{1}H NMR:

($CDCl_3$) δ = 7.602 (d, 2H), 7.410 (bs, 1H), 7.342 (t, 2H), 7.108 (t, 1H), 4.769 (s, 2H), 4.406 (s, 2H), 4.237 (s, 5H).

1,3,5-Triformylphloroglucinol. A portion of phloroglucinol (10.00 g, 0.0793 mol) added to a 1L 3-necked round bottom flask fitted with a condenser. A portion of hexamethylenetetramine (42.00 g, 0.3 mol) was added and the reaction vessel was purged with nitrogen. A portion of trifluoroacetic acid (80 mL, 2.42 mol) was added to the mixture at 0 °C to afford a bright yellow heterogeneous mixture, which was heated at reflux for 2.5 h. While heating, the color of the mixture darkened significantly to an amber color. The reaction flask was removed from heat and cooled to 0 °C for 5 min and 2N HCl (600 mL). The mixture was heated at reflux for 60 min. After standing overnight, an orange liquid and white solid suspension remained. The solid was collected by filtration (4.8 g) and sublimed to afford desired product (1.05 g, 6.3%).

Future Work

We are confident that we can use the redox active properties of TTF to our advantage in a variety of systems. Once the TTF protected amine is made, condensation to the 1,3,5-triformylphloroglucinol core should be straight forward. Tautomerization of the trifunctionalized core should occur at a single, well defined, oxidation state, although it is still unknown at which state it will be (Scheme 7).



Scheme 7. Tautomerization may occur at any of the possible +6 oxidation states.

The tautomerization would be unambiguously observed as a major change in the IR spectrum from carbonyl to alcohol at one step. We can then also modify the α-hydrogen position of the core by replacing it with electron withdrawing or donating groups to probe any effect it may have on at which oxidation state tautomerization occurs.